CAPA within the Pharmaceutical Quality System

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Agenda

- **What is CAPA?**
- **Other Industries**
- **Case Study:**
  How CAPA developed in Biotech
- **The Desired State**
- **Enablers for an Effective CAPA System**
- **Lessons Learned**
- **Summary**

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What is CAPA per ICH Q10?
(Corrective and Preventive Actions)

A structured approach to the investigation process should be used with the objective of determining the root cause.

The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9.

CAPA methodology should result in product and process improvements and enhanced product and process understanding.

Q10 Definition for Corrective Action

- **Corrective Action:** Action to eliminate the cause of a detected nonconformity or other undesirable situation.

  NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Q10 Definition for Preventive Action

- **Preventive Action:** Action to eliminate the cause of a potential nonconformity or other undesirable potential situation.

  NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

A mature quality system detects problems before they occur and then prevents the problems

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Electronics Industry Challenges Drove Continuous Improvement

- Extreme cost pressures
- Product and designs are easy to copy
- Material & capital costs
- Consumers demand reliability

... Adopted six sigma to meet these challenges …

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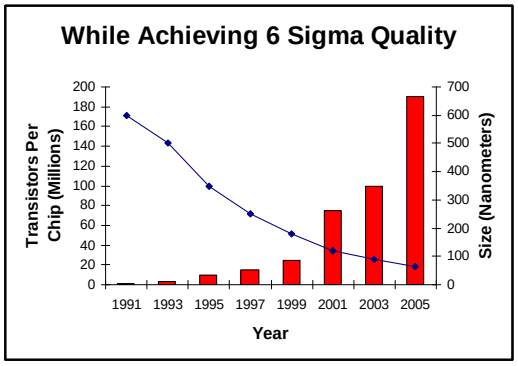
Power of Process Improvement: The Electronics Industry



Performance & Quality Improvements → More Powerful & Reliable Devices → Tremendous Consumer Value

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The Auto Industry Challenges Drove Quality Improvements

- Planned obsolesce
- New competition
- Loss of market share
- Improved product quality

… But …

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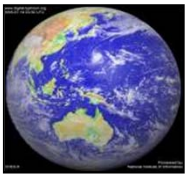
If the auto industry had achieved similar improvements in the last 30 years...

… a Rolls Royce would cost only $50



… it would circle the globe twice on only 0.5 gallons of gas

… its top speed would be 2.5 million mph!

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Source: ICE Cost Effective IC Manufacturing

So Why Have Pharmaceuticals Not Achieved 6 Sigma Manufacturing?

	Sigma	ppm Defects	Yield
	2σ	308,537	69.2%
Biotech	3σ	66,807	93.3%
Pharma	4σ	6,210	99.4%
	5σ	233	99.98%
Electronics & Auto	6σ	3.4	99.99966%

"We achieve 6 sigma quality using 3 sigma processes"

"Quality is free at the end of the day, if you can get it right"

Source: PriceWaterhouseCoopers Presentation, FDA Science Board Meeting November 16, 2001

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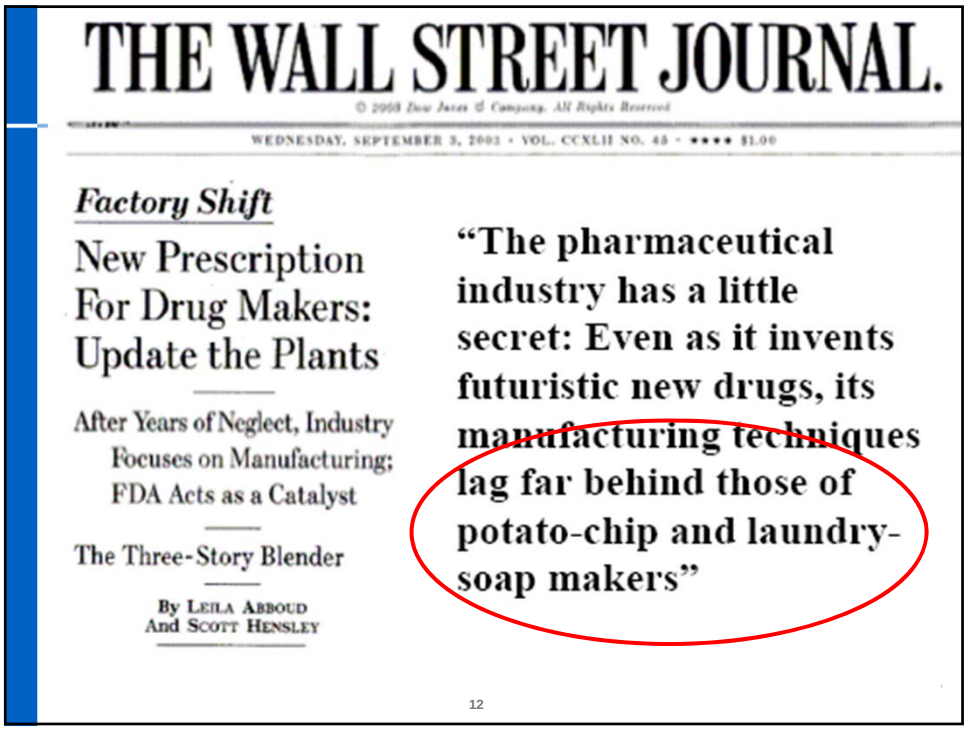

THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 · VOL. CCXLII NO. 45 · ★★★★ $1.00

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud And Scott Hensley

"The pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers"

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What Keeps us from Changing

- Victims of our own success
- Products have strong patent protection
- We are isolated from economic cycles
- Regulatory systems promoted and encouraged an inspect and test quality system

There has not been sufficient pain creating pressure to force us to change!

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Is the Perfect Storm Brewing?

Electronics Industry Dynamics		Bio & Pharm Similarities
Extreme cost pressures	→	**Health Care Cost Concerns**
Easy to copy	→	**Look-a-Likes**
Material Costs	→	**Capital Intensive**
Reliability	→	**Safety**

A major storm is around the corner. Successful companies will batten down the hatches **today** to weather the storm tomorrow.

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Stuff Happens

How we deal with issues will make or break us! A robust CAPA process will help make good decisions easier!

The CAPA Journey Provides Many Lessons Learned

Prior to 1995
Deviation Reports
Report only major departures from procedure

Inspections

1995 to 2001
Quality Incidents
Expand scope to include more types of discrepancies

Inspections

2001 to 2006
Non-conformances
Expand scope; emphasize investigation quality; little risk management

More trending & holistic review of data identifying preventive actions

Today
Non-conformances
Risk based, Strong Governance with action oriented management review

Risk Based Approach Implemented

Management Review & Quality Plan

Overwhelmed the System with Numbers

Basics of Today's CAPA System

- Today the majority of CAPAs start with exceptions and are "Manufacturing Focused"
  - Deviations, Non-Conformances, Annual Product Review, Management Review, Complaints, Risk Management, Validation, etc
- Patient focused
  - Risk based
  - Effort, resources and timelines proportional to patient risk

Basics of Today's CAPA System

- Strong Governance
  - Vet appropriateness of corrective actions and timelines
- Management Review
  - Defined metrics plan
  - Escalation process
  - Management commitment

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ICH Q10 Recommends a Product Lifecycle Approach

Table II: Application of Corrective Action and Preventive Action System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward, and continual improvement.	CAPA should be used, and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered, as well as other products that might be affected.

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The Future

- More CAPAs will be based on non-exception type data such as:
  - Data trending and holistic data reviews
  - Continuous Improvement Projects
  - Industry and Regulatory Surveillance
  - Cost of Quality Model
  - Implement CAPA earlier in the development process

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ICH Q10 Require that Management have a formal process for reviewing the QS …

The review should include:

(a) Measurement of achievement of pharmaceutical quality system objectives

(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:

(1) Complaint, deviation, CAPA & change management…

Management Support and Management Review are Critical for an Effective CAPA Process.

Don't Forget that You Also Need

- Robust business process
- Standard methodology
- Information system
- Effective Training

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Lessons Learned

Law of Unintended Consequences

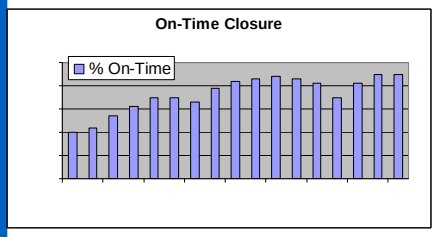
- **Numbers can overwhelm** → **Risk Based**
- **Artificial timelines** → **Realistic dates & interim reports**
- **Metrics & bad behaviors** → **Choose right metrics**

These three unintended consequences are the major reasons that CAPA systems have failed

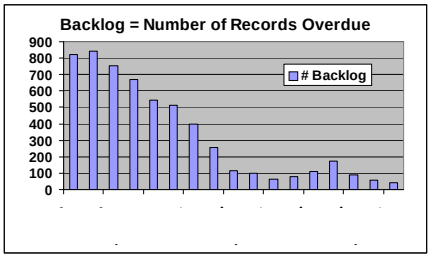
Lessons Learned

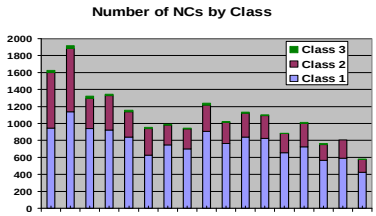
- Use a systematic approach
  - Have a standard tool
  - But choose the right tool for the job
- Monitor metrics closely (Management Review)
  - Only need a few critical metrics
  - Keep metrics simple
  - Use metrics to drive the right behaviors
  - Build in checks and balances
- Strong governance

Our Performance Metrics Greatly Improved



- Management Review Identified gaps
- Redeployed the best resources
- Quality and timeliness improved
- Faster root cause identification leading to more effective corrective & preventive actions
- Fewer significant & repetitive deviations





Investigation and CAPA performance significantly improved

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Summary

- Remember stuff will and does happen
- CAPA is an extremely valuable tool for continuous improvement
- Implement risk management and focus on the important issues first
- As professionals we should strive to prevent significant problems
- Use metrics to monitor performance
- Beware of unintended consequences

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Thank You

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